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10/823,682	04/14/2004	Michel Perricaudet	EX95001-US-A	5373

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EXAMINER	
CHEN, SHIN LIN	
ART UNIT	PAPER NUMBER
1632	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/06/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/823,682	PERRICAUDET ET AL.	
	Examiner	Art Unit	
	Shin-Lin Chen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 January 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-44* is/are pending in the application.

4a) Of the above claim(s) *6,27,35 and 37-44* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,7-26,28-34 and 36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *14 April 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4-14-04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election of group I, claims 1-5, 7-26 and 28-37, in the reply filed on 1-10-07 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

2. Claims 6, 27 and 38-44 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 1-10-07.

It is noted that applicants elected group I and the species of "antibody", "anti-CD4", and "aFGF". Since claims 35 and 37 read on "p53" rather than "aFGF", therefore, claims 35 and 37 will not be examined by examiner. Claims 1-44 are pending. Claims 1-5, 7-26, 28-34 and 36 are under consideration.

Specification

3. The disclosure is objected to because of the following informalities: The term "CLAIMS" on page 44 of the specification is improper. Changing the term "CLAIMS" to "We claim:" or "What is claimed is:" would be remedial.

Appropriate correction is required.

Priority

4. Acknowledgment is made of applicant's claim for foreign priority based on an application filed in FRANCE 95/01662 on 2-14-95. It is noted, however, that applicant has not filed a

certified copy of the foreign application as required by 35 U.S.C. 119(b). Since no certified copy of the foreign application has been received and no translation of said foreign application has been submitted, therefore, the priority date of the foreign application FRANCE 95/01662 is not granted. The effective priority date of the instant invention is 2-12-96.

Information Disclosure Statement

5. The information disclosure statement filed 4-14-04 fails to comply with 37 CFR 1.98(a)(1), which requires the following: (1) a list of all patents, publications, applications, or other information submitted for consideration by the Office; (2) U.S. patents and U.S. patent application publications listed in a section separately from citations of other documents; (3) the application number of the application in which the information disclosure statement is being submitted on each page of the list; (4) a column that provides a blank space next to each document to be considered, for the examiner's initials; and (5) a heading that clearly indicates that the list is an information disclosure statement. The information disclosure statement has been placed in the application file, but the information referred to therein has not been considered. There are **two pages of form PTO-892** in the submitted IDS, which is improper. The IDS must have **(3) the application number of the application in which the information disclosure statement is being submitted on each page of the list; (4) a column that provides a blank space next to each document to be considered, for the examiner's initials; and (5) a heading that clearly indicates that the list is an information disclosure statement.** Appropriate correction is required.

6. The information disclosure statement filed 4-14-04 fails to comply with 37 CFR 1.98(a)(2), which **requires a legible copy** of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the information referred to therein has not been considered.

The listing of references in the Search Report is not considered to be an information disclosure statement (IDS) complying with 37 CFR 1.98. 37 CFR 1.98(a)(2) requires a legible copy of: (1) each foreign patent; (2) each publication or that portion which caused it to be listed; (3) for each cited pending U.S. application, the application specification including claims, and any drawing of the application, or that portion of the application which caused it to be listed including any claims directed to that portion, unless the cited pending U.S. application is stored in the Image File Wrapper (IFW) system; and (4) all other information, or that portion which caused it to be listed. In addition, each IDS must include a list of all patents, publications, applications, or other information submitted for consideration by the Office (see 37 CFR 1.98(a)(1) and (b)), and MPEP § 609.04(a), subsection I. states, "the list ... must be submitted on a separate paper." Therefore, the references cited in the Search Report have not been considered. Applicant is advised that the date of submission of any item of information or any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the IDS, including all "statement" requirements of 37 CFR 1.97(e). See MPEP § 609.05(a).

Claim Rejections - 35 USC § 112

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 2, 3, 21, 22, 34 and 36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The phrase "selected from cyclosporine, FK506, azathioprine, a corticosteroid, or monoclonal antibody or polyclonal antibody" in claims 2 and 21 is vague and renders the claims indefinite. It is unclear whether it is selected from "cyclosporine, FK506, azathioprine, a corticosteroid", or selected from "cyclosporine, FK506, azathioprine, a corticosteroid, and monoclonal antibody" or selected from "cyclosporine, FK506, azathioprine, a corticosteroid, monoclonal antibody and polyclonal antibody". Claim 3 depends from claim 2. Claim 22 depends from claim 21.

The phrase "selected from the group anti-CD4...and –LFA-1 antibodies, and CTLA4Ig" in claims 3 and 22 is vague and renders the claims indefinite. It is unclear whether the "CTLA4Ig" is included in the group or not. It is also unclear whether the group "consisting of" or "comprising" the components recited in the claims.

The term "CD4" in claims 3 and 22 is vague and renders the claims indefinite. The term "CD4" is an abbreviation that can stand for various meanings. It is unclear what meaning is intended. Spelling out the term "CD4" would be remedial.

The term "ICAM-1" in claims 3 and 22 is vague and renders the claims indefinite. The term "ICAM-1" is an abbreviation that can stand for various meanings. It is unclear what meaning is intended. Spelling out the term "ICAM-1" would be remedial.

The term "LFA-1" in claims 3 and 22 is vague and renders the claims indefinite. The term "LFA-1" is an abbreviation that can stand for various meanings. It is unclear what meaning is intended. Spelling out the term "LFA-1" would be remedial.

The term "B7" in claims3 and 22 is vague and renders the claims indefinite. The term "B7" is an abbreviation that can stand for various meanings. It is unclear what meaning is intended. Spelling out the term "B7" would be remedial.

The term "CTLA4Ig" in claims 3 and 22 is vague and renders the claims indefinite. The term "CTLA4Ig" is an abbreviation that can stand for various meanings. It is unclear what meaning is intended. Spelling out the term "CTLA4Ig" would be remedial.

The term "aFGF" in claims 34 and 36 is vague and renders the claims indefinite. The term "aFGF" is an abbreviation that can stand for various meanings. It is unclear what meaning is intended. Spelling out the term "aFGF" would be remedial.

The term "bFGF" in claims 34 and 36 is vague and renders the claims indefinite. The term "bFGF" is an abbreviation that can stand for various meanings. It is unclear what meaning is intended. Spelling out the term "bFGF" would be remedial.

Claim Rejections - 35 USC § 112

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 1-5, 7-26, 28-34 and 36 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of decreasing CD4+, CD3+ and CD8+ T

cells by the combination of anti-CD3 or anti-CD4 antibody with Ad-βgal-gp19K expressing gp19K protein of adenovirus, decreasing cytotoxic activity of splenocytes, isolated from animals treated with anti-CD4 antibody and Ad-βgal-gp19K, on p815-β-gal target cells expressing β-galactosidase, and prolonging the expression of β-gal in a liver of a mouse with the combination of anti-CD4 antibody and Ad-βgal-gp19K, does not reasonably provide enablement for a composition comprising any immunosuppressive agent, such as anti-CD4 antibody, and a recombinant adenovirus containing a first recombinant DNA encoding a therapeutic protein, such as aFGF, and a second recombinant DNA encoding an adenoviral gp19k protein, and a method for expression of a sequence of interest by using said composition. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 1-5, 7-26, 28-34 and 36 are directed to a composition comprising an immunosuppressive agent, such as anti-CD4 antibody, and a recombinant adenovirus comprising a first recombinant DNA and a second recombinant DNA, wherein the first recombinant DNA encoding a protein, such as aFGF protein as elected, and the second recombinant DNA containing a sequence encoding an adenoviral gp19k protein, and a method for expressing a sequence of interest comprising consecutively or simultaneously administering said immunosuppressive agent (e.g. anti-CD4 antibody) and said recombinant adenovirus into a subject. Claims 18 and 24 specify the sequence coding for an adenoviral gp19k protein contains one or more point mutations compared to the wild type human Ad5 adenovirus sequence and the gp19k protein retains an immunosuppressive activity.

Claims 1-5, 7-26, 28-34 and 36 encompass the use of any immunosuppressive agent, such as the elected anti-CD4 antibody, and a first recombinant DNA encoding a protein, such as aFGF protein, for immunosuppression in vivo. The specification of the present application only discloses decreasing CD4+, CD3+ and CD8+ T cells by the combination of anti-CD3 or anti-CD4 antibody with Ad-βgal-gp19K expressing gp19K protein of adenovirus, and decreasing cytotoxic activity of splenocytes, isolated from animals treated with anti-CD4 antibody and Ad-βgal-gp19K, on p815-β-gal target cells expressing β-galactosidase, and prolonging the expression of β-gal in a liver of a mouse with the combination of anti-CD4 antibody and Ad-βgal-gp19K.

The specification states "[t]he present invention realtes to the field of gene therapy and in particular to the use of adenovirus for expressing a therapeutic gene of interest. It relates, more specifically, to a novel method for treating pathologies of genetic origin, which method is based on the combined use of two types of therapeutic agents." (specification, p. 1, first paragraph). The claims read on gene therapy in vivo in light of the specification. B-gal was known in the art at the time of the invention as a marker gene rather than a therapeutic gene. The specification of the present application fails to provide adequate guidance and evidence that an adenovirus vector as claimed in the present application expressing a gene of interest, such as aFGF, and an adenoviral gp19k protein as separate proteins or as a fusion protein in combination with an immunosuppressive agent, such as anti-CD4 antibody could provide therapeutic effects for a gene therapy in a subject *in vivo*. The specification also fails to provide adequate guidance and evidence for the correlation of a specific gene of interest, such as aFGF, with a particular disease

or disorder such that the administration of the adenovirus expressing said gene of interest would provide therapeutic effects for a gene therapy in a subject *in vivo*.

The state of the prior art for gene therapy was not well developed and was highly unpredictable at the time of the invention. Verma et al., Sept. 1997 (Nature, Vol. 389, pages 239-242) reviews vectors known in the art for use in gene therapy and discusses problems associated with each type of vector. The teachings of Verma indicate a resolution to vector targeting has not been achieved in the art (see entire article). Verma also teaches appropriate regulatory elements may improve expression, but it is unpredictable what tissues such regulatory elements target (page 240, sentence bridging columns 2 and 3). Verma states that "The Achilles heel of gene therapy is gene delivery, and this is the aspect that we will concentrate on here. Thus far, the problem has been an inability to deliver genes efficiently and to obtain sustained expression...The use of viruses (viral vectors) is powerful technique, because many of them have evolved a specific machinery to deliver DNA to cells, However, humans have an immune system to fight off the virus, and our attempts to deliver genes in viral vectors have been confronted by these host responses." (e.g. p. 239, column 3). For instance, numerous factors complicate the gene therapy art which have not been shown to be overcome by routine experimentation. Eck et al., 1996 (Goodman & Gilman's The Pharmacological Basis of Therapeutics, McGraw-Hill, New York, p. 77-101) explains that the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, and the rate of degradation of the DNA are all important

factors for successful gene transfer *in vivo*. These factors differ dramatically based on the vector used, and the disease being treated (e.g. bridging pages 81-82).

In addition, Gorecki, 2001 (Expert Opin. Emerging Drugs, 6(2): 187-198) reports that "the choice of vectors and delivery routes depends on the nature of the target cells and the required levels and stability of expression" for gene therapy, and obstacles to gene therapy *in vivo* include "the development of effective clinical products" and "the low levels and stability of expression and immune responses to vectors and/or gene products" (e.g. abstract). Thus, administration route plays an important role in gene transfer efficiency. There is no evidence of record that shows that administration of the claimed composition expressing a gene of interest, such as aFGF, to a subject via various administration routes would be able to obtain sufficient and prolonged expression at various target sites so as to provide therapeutic effects for a gene therapy of a particular disease in said subject *in vivo*.

The specification only discloses the prolonged expression of β-gal in the liver of a mouse but fails to provide adequate guidance and evidence for the prolonged expression of any therapeutic gene in organs other than liver in a subject *in vivo*. Different organs, tissues or targeted site could vary physically and biologically such that the expression of a gene *in vivo* also could vary depending on the site being targeted. It is unclear whether the adenoviral gp19k gene and anti-CD4 antibody could provide sufficient expression in a particular organ, tissue or targeted site such as to achieve prolonged expression of a gene of interest so as to provide therapeutic effect in a subject for a gene therapy of a particular disease or disorder.

Claims 18 and 24 read on using the sequence coding for an adenoviral gp19k protein contains one or more point mutations compared to the wild type human Ad5 adenovirus

sequence and the gp19k protein retains an immunosuppressive activity. The claims encompass numerous different structural variants of an adenoviral gp19k protein.

It was known in the art that the amino acid sequence of a polypeptide determines its structural and functional properties (including half-life), and predictability of which amino acid(s) can be removed from or added to a polypeptide's sequence and still result in similar activity or result in stabilization of the protein is extremely complex, and well outside the realm of routine experimentation. Rudinger, 1976 (Peptide Hormones, Parsons, University Park Press, Baltimore, p. 1-7) points out that "The significance of particular amino acids and sequences for different aspects of biological activity cannot be predicted *a priori* but must be determined from case to case by painstaking experimental study" (e.g. p. 6). Kaye et al., 1990 (Proc. Natl. Acad. Sci. USA, Vol. 87, pp. 6922-6926) discloses that a single amino acid substitution results in a retinoblastoma protein defective in phosphorylation and oncoprotein binding (e.g. title). Skolnick et al., 2000 (Trends in Biotech, Vol. 18, p. 34-39) states "Sequence-based methods for function prediction are inadequate because of the multifunctional nature of proteins. However, just knowing the structure of the protein is also insufficient for prediction of multiple functional sites. Structural descriptors for protein functional sites are crucial for unlocking the secrets in both the sequence and structural-genomics projects" (e.g. abstract). Skolnick further states that "Knowing a protein's structure does not necessarily tell you its function" and "Because proteins can have similar folds but different functions, determining the structure of a protein may or may not tell you something about its function" (e.g. p. 36, box 2).

Further, Lollar et al., 1992 (The Journal of Biological Chemistry, Vol. 267, No. 33, pp. 23652-23657), reports that "[p]orcine HC/human LC (pHC/hLC) fVIII had 44-fold higher

coagulant activity than reconstituted human fVIII (hHC/hLC), 40-fold higher activity than hHC/pLC), and slightly (1.4-fold) higher activity than reconstituted porcine fVIII (pHC/pLC)" and "A2 subunit itself is responsible for the difference" (e.g. abstract). It appears that factor VIII proteins derived from different organisms have diverse amino acid sequences and could have different biological activities. It is apparent that protein function was unpredictable from mere amino acid sequence at the time of the invention. Even the same kind of protein, such as factor VIII protein, derived from different organisms would have diversified biological functions or activities. One skilled in the art at the time of the invention could not determine the biological function and activity of a protein without trail and error experimentation.

For the reasons discussed above, it would have required undue experimentation for one skilled in the art at the time of the invention to practice over the full scope of the invention claimed. This is particularly true given the nature of the invention, the state of the prior art, the breadth of the claims, the amount of experimentation necessary, the level of ordinary skill which is high, the working examples provided and scarcity of guidance in the specification, and the unpredictable nature of the art.

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

13. Claims 1-5, 7-17, 19-23, 25, 26, 28-34 and 36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Leibowitz et al., 1994 (WO 94/16065, IDS) in view of Pearson et al., 1993 (Clinical Experimental Immunology, Vol. 92, p. 211-217) and Nabel et al., 1994 (Annals New York Academy of Sciences, Vol. 714, p. 247-252).

Claims 1-5, 7-17, 19-23, 25, 26, 28-34 and 36 are directed to a composition comprising an immunosuppressive agent, such as anti-CD4 antibody, and a recombinant adenovirus comprising a first recombinant DNA and a second recombinant DNA, wherein the first recombinant DNA encoding a protein, such as a aFGF protein as elected, and the second recombinant DNA containing a sequence encoding an adenoviral gp19k protein, and a method for expressing a sequence of interest comprising consecutively or simultaneously administering said immunosuppressive agent (e.g. anti-CD4 antibody) and said recombinant adenovirus into a subject. Claims 7-13 and 28-30 specify the first and second recombinant DNAs constitute a single transcription entity, use same promoter, inserted in the same orientation, or inserted into different sites in the adenovirus genome. Claims 31-33 specify the immunosuppressive agent is administered both before and after administration of the adenovirus or administered

simultaneously, and the adenovirus is administered by injection. Claims 34 and 36 specify the first recombinant DNA comprises a coding sequence for aFGF.

Leibowitz teaches construction of a recombinant Ad5 adenovrius vector containing adenoviral E19 (i.e. gp19K) coding sequence operably linked to a promoter and infection of a wide variety of donor cells with said adenovirus vector to alter the presentation of MHC class I cell surface antigen on these cells and thereby allow introduction of these cells into a recipient organism while reducing transplant rejection by the recipient organism's immune system (e.g. abstract, p. 9, 10). Leibowitz teaches preparation of replication deficient recombinant adenoviral vector lacking viral E1 region (e.g. p. 9). Leibowitz also teaches a method of effecting gene therapy in a recipient organism by transplanting into said recipient organism cells expressing a gene product of interest for an abnormal genetic condition and said transplanted cells have been treated with E19pk protein to alter the presentation of MHC class I cell surface antigen to reduce transplant rejection by the recipient organism's immune system (e.g. p. 35).

Leibowitz does not teach combination of an immunosuppressive agent, such as anti-CD4 antibody, with a recombinant adenovirus vector expressing a sequence of interest, such as aFGF, and an adenovirus gp19k protein in a composition or for a method of expressing the sequence of interest by using said composition.

Pearson teaches using anti-CD4 MoAb for the prolongation of cardiac allograft survival in adult mice and demonstrates that very low doses of anti-CD4 MoAb, YTS191.1, were able to induce prolonged allograft survival when administered perioperatively, and the immunosuppression induced by the anti-CD4 MoAb is not antigen-specific (e.g. abstract).

Nabel teaches using recombinant adenoviral vector expressing FGF-1 for gene transfer into vascular cells and discloses the problem of host immune response to the adenoviral vector for gene transfer (e.g. p. 248, 249).

It would have been obvious for one of ordinary skill at the time of the invention to combine the immunosuppressive agent with an adenovirus vector containing a sequence of interest and coding sequence for gp19k protein in a composition and the use of said composition for expressing the sequence of interest because immunosuppressive agent such as anti-CD4 antibody can induce prolonged allograft survival in adult mice and E19pk protein can alter the presentation of MHC class I cell surface antigen to reduce transplant rejection by the recipient organism's immune system and combining said agent and adenovirus vector would enhance their immunosuppressive effects. The arrangement of the sequence of interest and E19 gene in a vector, e.g. in a single transcriptional entity or in the same orientation, and the sequential order of administering immunosuppressive agent and adenovirus are routine optimization of a result-effective variable and is obvious to a person of ordinary skill.

One having ordinary skill at the time the invention was made would have been motivated to generate a composition comprising an immunosuppressive agent such as anti-CD4 antibody and an adenoviral vector containing a sequence of interest and coding sequence for gp19k protein and the use of said composition for expressing the sequence of interest in order to reduce transplant rejection by the recipient organism's immune system by altering the presentation of MHC class I cell surface antigen on donor cells or to effect gene therapy in a recipient organism as taught by Leibowitz or to induce prolonged allograft survival in adult mice as taught by Pearson with reasonable expectation of success. Further, the immune response triggered by

adenovirus vector as taught by Nabel would also motivate one ordinary skill to combine the immunosuppressive agent and the adenoviral vector set forth above in order to suppress the host immune response while using adenoviral vector for gene transfer.

14. Claims 1-5, 7-17, 19-23, 25, 26 and 28-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Leibowitz et al., 1994 (WO 94/16065, IDS) in view of Wilson et al., 1999 (US patent No. 5,872,154).

Claims 1-5, 7-17, 19-23, 25, 26 and 28-33 are directed to a composition comprising an immunosuppressive agent, such as anti-CD4 antibody, and a recombinant adenovirus comprising a first recombinant DNA and a second recombinant DNA, wherein the first recombinant DNA encoding a protein and the second recombinant DNA containing a sequence encoding an adenoviral gp19k protein, and a method for expressing a sequence of interest comprising consecutively or simultaneously administering said immunosuppressive agent (e.g. anti-CD4 antibody) and said recombinant adenovirus into a subject. Claims 7-13 and 28-30 specify the first and second recombinant DNAs constitute a single transcription entity, use same promoter, inserted in the same orientation, or inserted into different sites in the adenovirus genome. Claims 31-33 specify the immunosuppressive agent is administered both before and after administration of the adenovirus or administered simultaneously, and the adenovirus is administered by injection.

Leibowitz teaches construction of a recombinant Ad5 adenovrius vector containing adenoviral E19 (i.e. gp19K) coding sequence operably linked to a promoter and infection of a wide variety of donor cells with said adenovirus vector to alter the presentation of MHC class I

cell surface antigen on these cells and thereby allow introduction of these cells into a recipient organism while reducing transplant rejection by the recipient organism's immune system (e.g. abstract, p. 9, 10). Leibowitz teaches preparation of replication deficient recombinant adenoviral vector lacking viral E1 region (e.g. p. 9). Leibowitz also teaches a method of effecting gene therapy in a recipient organism by transplanting into said recipient organism cells expressing a gene product of interest for an abnormal genetic condition and said transplanted cells have been treated with E19pk protein to alter the presentation of MHC class I cell surface antigen to reduce transplant rejection by the recipient organism's immune system (e.g. p. 35).

Leibowitz does not teach combination of an immunosuppressive agent, such as anti-CD4 antibody with a recombinant adenovirus vector expressing a sequence of interest and an adenovirus gp19k protein in a composition or for a method of expressing the sequence of interest by using said composition.

Wilson teaches co-administration of a recombinant adenovirus and a selected modulator to reduce an immune response to the recombinant adenovirus (e.g. abstract) and the immune modulator may be administered prior to, or concurrently with, the viral vector bearing a transgene to be delivered (e.g. column 2, lines 10-12). The immune modulator is defined as "an agent capable of inhibiting the formation of neutralizing antibodies directed against the recombinant viral vector or capable of inhibiting cytolytic T lymphocyte (CTL) elimination of the vector" (e.g. column 3, second paragraph). An example of the immune modulator is antibody that binds to CD4 protein (e.g. column 4, lines 25-28).

It would have been obvious for one of ordinary skill at the time of the invention to combine the immunosuppressive agent with an adenovirus vector containing a sequence of

interest and coding sequence for gp19k protein in a composition and the use of said composition for expressing the sequence of interest because Leibowitz teaches using adenoviral vector expressing gp19k protein to reduce transplant rejection by the recipient organism's immune system and Wilson teaches co-administration of a recombinant adenovirus and a selected modulator, such as anti-CD4 antibody, to reduce an immune response to the recombinant adenovirus. The arrangement of the sequence of interest and E19 gene in a vector, e.g. in a single transcriptional entity or in the same orientation, and the sequential order of administering immunosuppressive agent and adenovirus are routine optimization of a result-effective variable and is obvious to a person of ordinary skill.

One having ordinary skill at the time the invention was made would have been motivated to generate a composition comprising an immunosuppressive agent such as anti-CD4 antibody and an adenoviral vector containing a sequence of interest and a coding sequence for gp19k protein and the use of said composition for expressing the sequence of interest in order to reduce transplant rejection by the recipient organism's immune system by altering the presentation of MHC class I cell surface antigen on donor cells or to effect gene therapy in a recipient organism as taught by Leibowitz or to reduce an immune response to the recombinant adenovirus as taught by Wilson with reasonable expectation of success.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (571) 272-0726. The examiner can normally be reached on Monday to Friday from 9:30 am to 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272-4517. The fax phone number for this group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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PRIMARY EXAMINER